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Increasing synthetic efficiency *via* direct C–H functionalization: formal synthesis of an inhibitor of botulinum neurotoxin†‡

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A new and efficient scheme for the synthesis of one of the best known inhibitors of botulinum neurotoxin serotype A (BoNTA) is reported herein. The synthetic route involves two palladium-catalyzed C–H functionalization reactions, formally activating three C–H bonds.

Botulinum neurotoxin serotype A (BoNTA) is a protein produced by a spore-forming bacteria called *Clostridium botulinum*. It is the world's most poisonous protein having a median lethal dose of approximately 1 ng/Kg.[1] The toxin is associated with numerous food-borne illnesses and is a potential bioweapon. Consequently, the synthesis of small molecule inhibitors of BoNTA is of high importance.[2,3] Previous work has shown that development of BoNTA inhibitors is particularly challenging because the enzyme-substrate interface is unusually large. Recently, Pang computationally docked potential inhibitors into the zinc endopeptidase active site of BoNTA and then synthesized and tested the best drug candidates (Fig. 1).[4–7] The best inhibitors consisted of two heterocyclic halves: a 2-phenlyindole and a 2-phenylthiophene (**1**, K_i = 15 μM).[6] Further computational and synthetic studies recently showed that further elaboration of the 2-aryl thiophene moiety provided increased BoNTA inhibition (**2**, K_i = 5.4 μM).[4]

In general, two synthetic strategies can be envisioned for the synthesis of these aryl substituted heterocycles (Scheme 1): the biaryl bond could be synthesized *via* an organometallic coupling or the heterocycle could be constructed *via* annulation of an aryl-substituted linear substrate. Pang and co-workers employed both of these paths by cyclizing a 2-alkylaniline to form the 2-arylindole substructure and by arylating a 2-bromothiophene in a Suzuki reaction.[4]

Contrastingly, Itahara developed a method for oxidatively coupling heteroarenes such as indoles, pyrroles and furans with benzene in the early 1980's.[8–10] These original reactions required superstoichiometric amounts of palladium acetate.

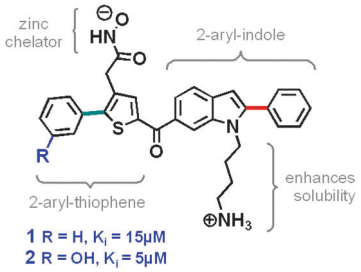

Fig. 1 Structure of thiophene-indole BoNTA inhibitors.

We and others have recently developed catalytic methods for directly arylating heterocycles involving either one or two C–H functionalizations.[11–16] These methods offer the benefit of greater step economy by using readily available hydrocarbon starting materials.[17,18] Herein, we present a novel method for synthesizing inhibitor **1** using two key palladium catalyzed C–H activation steps.

We have recently shown that electron-rich aromatic heterocycles and benzene-derived arenes can be oxidatively cross-coupled by palladium catalysis. For example, both we and the Fagnou group have shown that *N*-acetylindoles can be regioselectively coupled with benzene at either their 2- or 3-position depending on the nature of the oxidant chosen for the reaction.[19–23] We have extended this methodology to include *N*-alkylindoles, a considerably more challenging class of compounds due to their tendency to decompose in the oxidative reaction conditions. In particular, we have found that *N*-alkylindoles bearing electron-withdrawing groups provide high levels of regioselectivity, favoring the 2-aryl-product.[19] Consequently, **1** appeared to be an ideal target for the application of our oxidative coupling technology.

We commenced our study by attempting the oxidative arylation of the butylphthalimide protected ester indole **13**, but low regioselectivity was observed (**14**; 3 : 1, 2-Ph : 3-Ph), and the two regioisomers were inseparable by flash chromatography (Scheme 2). However, selective oxidative arylation of the SEM-protected indole **15**,[24] using catalytic palladium acetate ($PdOAc_2$) and silver acetate (AgOAc) as an oxidant, afforded **16** in a good yield with a 9 : 1 regioselectivity favoring arylation at the indole's 2-position, and these regiomers could be separated *via* flash chromatography. The optimal conditions contained a slight excess of AgOAc (3 equiv.) compared to pivalic acid (PivOH, 2.5 equiv.), which likely prevents the

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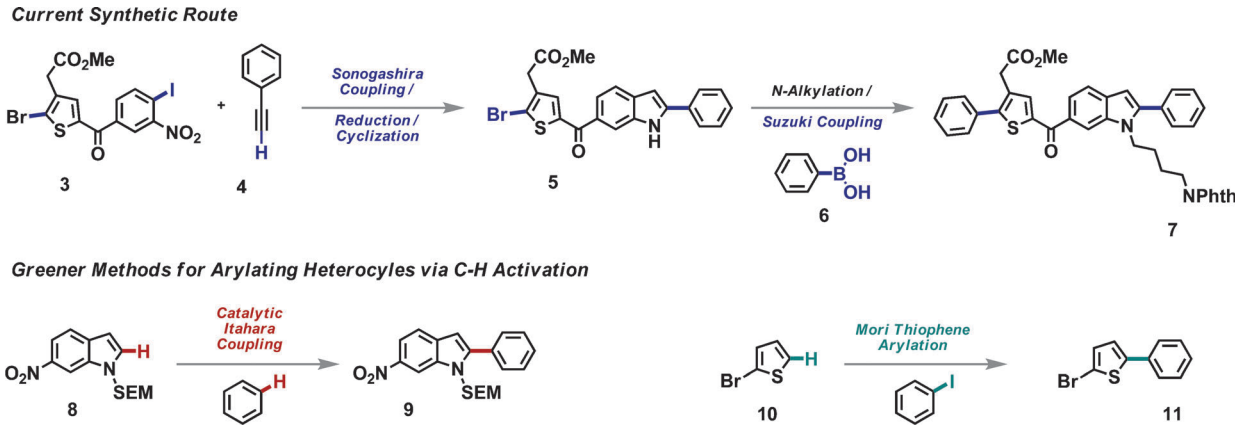
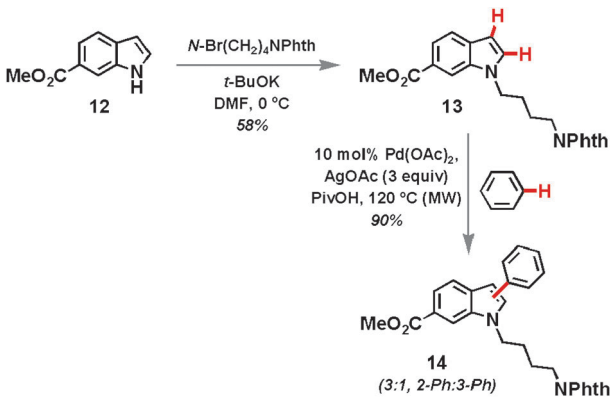
‡ Electronic supplementary information (ESI) available: Procedures for the synthesis of all new compounds and their characterization (^{1}H-NMR, ^{13}C-NMR, and mass spectra). See DOI: 10.1039/c1cc10755k



Scheme 1 Comparison of synthetic schemes for constructing arylated heterocycles.

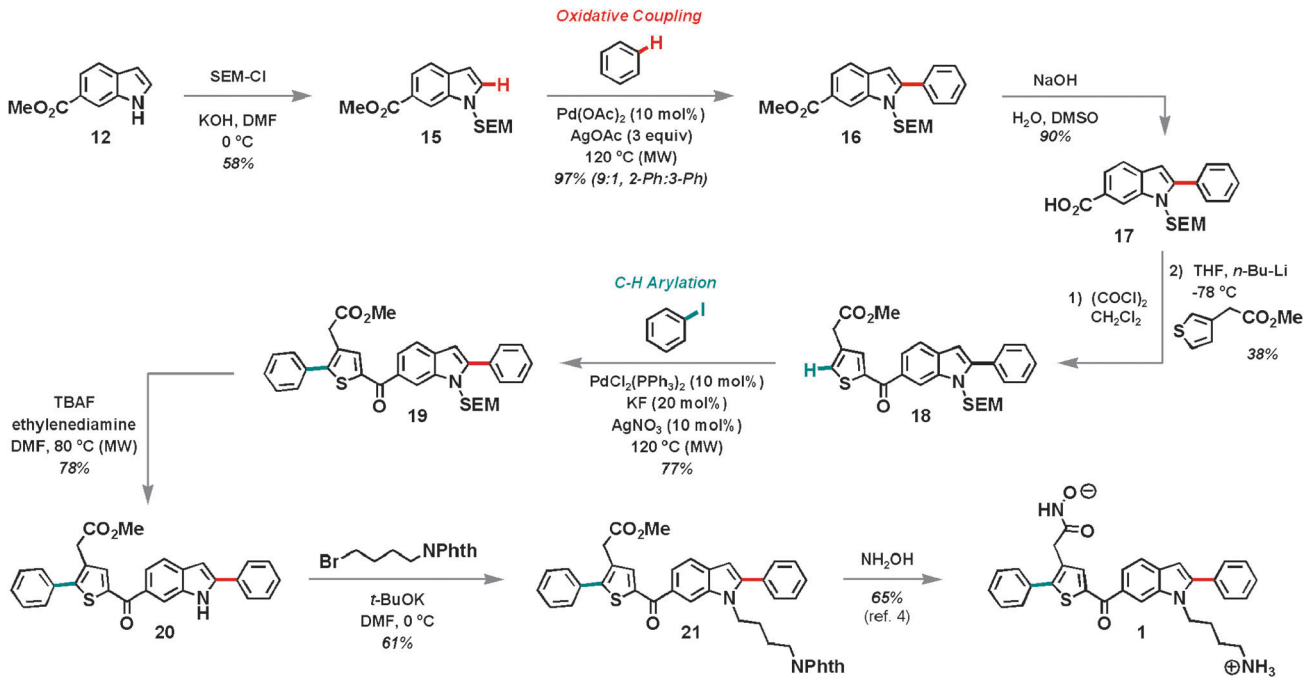


Scheme 2 Oxidative arylation of *N*-alkyl protected indole.

acid-promoted oxidative decomposition of the indole substrate and products (Scheme 3).[19]

Alkaline hydrolysis of **16** afforded the free acid **17** in a good yield. *In situ* conversion of **17** to the acid chloride, followed by Friedel–Crafts acylation, as described by Pang,[4] was attempted, but the desired ketone was not observed. Later, the acid chloride was reacted with the anion of methyl-3-thiophene-acetate to afford the desired product **18** in a modest 38% isolated yield. The isomer which is coupled at the thiophene's 2-position (proximal to the ester), was isolated as a minor product (6% yield). We attribute the selectivity favoring the desired product to steric factors (Scheme 3).

In an effort to expand our methodology to form biaryl C–C bonds by activating two C–H bonds, we initially attempted to oxidatively couple benzene to thiophene **18** using our earlier



Scheme 3 Synthetic scheme for BoNTA inhibitor **1**.

optimization studies as a guide,[19,22] but the starting material failed to convert. This may be the result of the ability of the thiophene to deactivate the palladium catalyst *via* coordination of its sulfur atom. However, using Mori's conditions, the C–H bond of the thiophene **18** was selectively arylated using both palladium and silver catalysts and iodobenzene as the arene source.[25] The SEM protecting group of compound **19** was cleaved by treatment with tetrabutylammonium fluoride (TBAF) in DMF to afford **20** and subsequent *N*-alkylation was carried out with *N*-(4-bromobutyl)-phthalimide in the presence of potassium *tert*-butoxide to afford the *N*-alkylindole **21**. Finally, the BoNTA inhibitor **1** was synthesized following the procedure of Pang by treating **21** with excess hydroxylamine, which simultaneously converts the methyl ester and phthalimide to hydroxamic acid and amine, respectively (Scheme 3).[4]

In conclusion, we have developed a novel synthetic route for the synthesis of an inhibitor of botulinum neurotoxin serotype A (BoNTA). The 4.6% overall yield is nearly identical to that which was reported by Pang, but the step economy of the overall synthesis has been increased due to the incorporation of reactions which do not rely on prefunctionalized starting materials; rather the biaryl C–C bonds were directly formed from the C–H bonds of simple arenes and heteroarenes. It should also be noted that the C–H functionalizing reactions are two of the highest yielding steps in this synthesis. While our initial attempts to form biaryl C–C bonds with thiophene-type substrates such as **18** were not successful, efforts in our laboratory are currently focused on expanding our oxidative coupling methods to encompass these and other classes of heteroarenes for application to the synthesis of more high-value targets.

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Notes and references

1 D. O. P. Fleming and D. L. Hunt, *Biological Safety: Principles and Practices*, ASM Press, 4th edn, 2006.
2 T. Cote, A. Mohan, J. Polder, M. Walton and M. Braun, *J. Am. Acad. Dermatol.*, 2005, **53**, 407–415.
3 K. R. Kessler and R. Benecke, *Neurotoxicology*, 1997, **18**, 761–770.
4 J. Tang, J. G. Park, C. B. Millard, J. J. Schmidt and Y. Pang, *PLoS One*, 2007, **2**, e761.
5 Y. Pang, A. Vummenthala, R. K. Mishra, J. G. Park, S. Wang, J. Davis, C. B. Millard and J. J. Schmidt, *PLoS One*, 2009, **4**, e7730.
6 J. G. Park, P. C. Sill, E. F. Makiyi, A. T. Garcia-Sosa, C. B. Millard, J. J. Schmidt and Y. Pang, *Bioorg. Med. Chem.*, 2006, **14**, 395–408.
7 Y. Pang, J. Davis, S. Wang, J. G. Park, M. P. Nambiar, J. J. Schmidt and C. B. Millard, *PLoS One*, 2010, **5**, e10129.
8 T. Itahara, *J. Chem. Soc., Chem. Commun.*, 1981, 254.
9 T. Itahara, K. Kawasaki and F. Ouseto, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3488–3493.
10 T. Itahara, *J. Org. Chem.*, 1985, **50**, 5272–5275.
11 G. P. McGlacken and L. M. Bateman, *Chem. Soc. Rev.*, 2009, **38**, 2447–2464.
12 X. Chen, K. Engle, D. Wang and J. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115.
13 L. Joucla and L. Djakovitch, *Adv. Synth. Catal.*, 2009, **351**, 673–714.
14 C. Li, *Acc. Chem. Res.*, 2009, **42**, 335–344.
15 B. Li, S. Yang and Z. Shi, *Synlett*, 2008, **2008**, 949–957.
16 D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238.
17 B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281.
18 R. A. Sheldon, *Pure Appl. Chem.*, 2000, **72**, 1233–1246.
19 S. Potavathri, K. C. Pereira, S. I. Gorelsky, A. Pike, A. P. LeBris and B. DeBoef, *J. Am. Chem. Soc.*, 2010, **132**, 14676–14681.
20 S. Potavathri, A. S. Dumas, T. A. Dwight, G. R. Naumiec, J. M. Hammann and B. DeBoef, *Tetrahedron Lett.*, 2008, **49**, 4050–4053.
21 D. R. Stuart, E. Villemure and K. Fagnou, *J. Am. Chem. Soc.*, 2007, **129**, 12072–12073.
22 T. A. Dwight, N. R. Rue, D. Charyk, R. Josselyn and B. DeBoef, *Org. Lett.*, 2007, **9**, 3137–3139.
23 D. R. Stuart and K. Fagnou, *Science*, 2007, **316**, 1172–1175.
24 Touré, B. S. Lane and D. Sames, *Org. Lett.*, 2006, **8**, 1979–1982.
25 K. Kobayashi, A. Sugie, M. Takahashi, K. Masui and A. Mori, *Org. Lett.*, 2005, **7**, 5083–5085.